REMARKS

Oath/Declaration:

The Office Action states that the current oath or declaration is defective, due to the presence of non-initialed and non-dated alterations were made to the oath or declaration. A new declaration meeting the requirements will be submitted in the near future.

Brief Description of the Drawings:

The Office Action states that the disclosure is objected to because there is no Brief Description of the Drawings. Applicant notes that a Brief Description of the Drawings is submitted herewith.

Rejections Under 35 U.S.C. §112:

The Office Action states that claims 43-62 are rejected under 35 U.S.C. §112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention. Specifically, with respect to claims 43-60, the Office Action states that claims 43, 59 and 60 are unclear due to uncertainty with the term "derivative" as used in the claims.

Without admitting to the propriety of the rejection for indefiniteness, applicants have amended claims 43, 59 and 60 to limit the term "derivative" to "acyl derivative." Applicant believes the scope of the amended claims is now clear.

The Office Action also states that claims 61-62 are unclear in that it is not apparent from the disclosure which of the disclosed compounds, with the exception of the elected compound 3, 7 diepi-casuarine, have the recited property of a Th-1-activating alkaloid that can be used in an amount effective to polarize the immune response to an antigen from a type 2 response toward a type 1 response. Applicants believe that the current amendments to the claims resolve any ambiguity regarding the scope of these claims.

The Office Action also states that claims 47, 48, 51 and 52 are rendered indefinite through the presence of the language "for example (e.g.)" because such language makes it unclear whether or not the limitations following that phrase are part of the claimed invention or

not. Applicant has amended claims 47, 48, 51 and 52 to resolve the ambiguity described in the Office Action.

Rejections Under 35 U.S.C. §103:

The Office Action states that claims 43-56 and 59-62 are rejected under 35 U.S.C. §103(a) as unpatentable over Watson et al. ("Polyhydroxylated alkaloids – natural occurrence and therapeutic applications"; 2001; Phytochemistry; 56; 265-295) in view of Clements et al. ("The global impact of vaccines containing aluminum adjuvants"; 2002; Vaccine 20: S24-S33). The Office Action states that Watson et al. teaches that "both swainsonine and nectrisine have the properties of immune stimulants" (please see page 9 of the Office Action). The Office action then states that swainsonine and nectrisine are structurally similar to casuarine and, as such, one of skill in the art would expect casuarine to have immune stimulant properties.

The Federal Circuit and its predecessor, the Court of Customs and Patent Appeals (C.C.P.A.) have each held that significant structural differences, such as those present in this case, preclude a finding of obviousness based on structural similarity. *See In re Grabiak*, 769 F.2d 729, 226 U.S.P.Q. 870 (Fed. Cir. 1985); *see also In re Grunwell*, 609 F.2d 486, 203 U.S.P.Q. 1055 (C.C.P.A. 1979). In particular, the Federal Circuit has said "...generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other." *Grabiak*, 769 F.2d at 731. The Court went on to say that there must be adequate support in the prior art for any differences in structure between the prior art structures and the structures at issue to support a prima facie case of obviousness. *Id.* at 732. Because the prior art did not provide any indication that substituting a sulfur atom for an oxygen atom would provide desired function to the resulting molecule, the Court held a finding of obviousness unsupportable. *Id.* The court found that differences existing between the ring structure of the prior art compounds and the compounds at issue was highly significant in finding a lack of structural similarity. *Id.* In *In re Grunwell*, the C.C.P.A. held that certain prior art compounds were not similar enough to the compound at issue to support a finding of obviousness because one compound was an alcohol and the other its ether. 609 F.2d at 491. The Court based its findings on the fact that the prior art references did not show any support for the substitution and thus could not support a prima facie case of obviousness. *Id.* The court did hold that one compound at issue was structurally similar enough to a prior art compound to be considered

structurally similar, where the compounds differed only in the addition of a methyl group to the compound at issue. *Id.* However, the Court was careful to note that such a substitution is not per se obvious and there were several factors in the prior art reference that suggested such a substitution would be acceptable, including an identical base ring structure and analogous physiological and psychological responses shown by both compounds. *Id.*

Respectfully, applicants assert that the amount of structural similarity between casuarine and either swainsonine or nectrisine is very low, and not sufficient to lead one of skill in the art to understand that casuarine or other compounds of the present invention would likely have immune stimulant properties. A critical difference between casuarine and either swainsonine or nectrisine is that the core ring structures are very different. Specifically, casuarine contains a bicyclic compound having two five-membered rings, while swainsonine contains a bicyclic ring structure having one *six*-membered ring and one five-membered ring;nectrisine is even further removed form casuarine, being only a monocyclic compound, having a single five-membered ring. Such stark differences in core structure precludes a finding of obviousness based on structural similarity between casuarine and either swainsonine or nectrisine. Further, the substituents attached to the core ring structure of each compound is significantly different. Casuarine has four hydroxyl groups and a hydroxymethyl group attached to the bicyclic ring structure, while swainsonine has only *three* hydroxyl groups attached to this ring structure and no hydroxymethyl group. Nectrisine is even further removed in light of its monocyclic structure and it includes only two hydroxyl groups and a hydroxymethyl group. In addition, there are significant differences between casuarine and both swainsonine and nectrisine with regard to the cis-trans orientation of the substituent groups. When the structural differences between casuarine and other compounds of the present invention and both swainsonine and nectrisine are considered, applicant respectfully asserts that no prima facie case of obviousness can be supported. Further, applicant asserts that one of skill in the art would not assume any functional similarity between casuarine and either swainsonine or nectrisine based on the demonstrated lack of structural similarity. Applicant also notes that the current amended claim set limits the scope of possible derivatives to acyl derivatives.

Moreover, even if either swainsonine or nectrisine were indeed structurally similar to casuarine or the other compounds of the present invention, Watson et al. does not teach that either swainsonine or nectrisine are capable of modulating an immune response from a type-2

response toward a type-1 response. The specificity of the immune response elicited by the compounds of the present invention is one of the novel features of the invention and cannot be ignored when making an obviousness analysis. Because nothing in the Watson reference even mentions the different classes of immune response (type 1 vs. type 2), applicant asserts that one of skill in the art would have had no indication that casuarine or any other compound of the present invention would have the effect of stimulating a type-1 immune response, or shifting an immune response from a type-2 response to a type-1 response.

With regard to the Clements et al. reference, the Office Action states that the reference teaches, among other things, that alum is a known adjuvant, which is used in combination with a variety of known vaccines to increase the effectiveness of the vaccines, and that there is a need for additional adjuvants (please see page 12 of the Office Action). The Office Action further states that, taken with the Watson et al reference described above, "the demonstrated increase of immune response when swainsonine or nectrisine is utilized would lead one of skill in the art to expect these compounds to have activity as adjuvants. Similarly, based on the common structure with casuarine would lead to a similar expectation for this compound possessing adjuvant activity."

As described above, applicant asserts that there is a lack of sufficient structural similarity between the compounds of the present invention and either swainsonine or nectrisine. Further, applicant asserts that one of skill in the art would not impute any property of either swainsonine or nectrisine to compounds of the present invention based on the teachings of Watson et al. Further, the Watson et al. reference does not provide any indication or motivation for one of skill in the art to believe that swainsonine or nectrisine, even if structural similarity were present, are capable of modulating an immune response from a type-2 immune response toward a type-1 immune response. Nothing in the Clements et al. reference remedies the deficiencies outlined above for the Watson et al. reference. As such, applicant respectfully requests that this rejection be withdrawn.

The Office Action further states that, with respect to claim 44, the recited property of stimulating IL-12 expression in vitro is taken to be a property possessed by the alkaloid compounds recited in the claims and thus characteristic of swainsonine and nectrisine as well. Applicant notes that amended claim 43 limits the scope of permissible derivatives and thus excludes both swainsonine and nectrisine from their scope.

The Office Action further states that claims 43-44, 49, 51, 53, 55 and 59-62 are rejected under 35 U.S.C. §103(a) as unpatentable over Watson et al., in view of Clements et al., and in further view of Bell et al. (Synthesis of Casuarines [Pentahydroxylated Pyrrolizidines] by Sodium Hydrogen Telluride-Induced Cyclisations of Azidomesylates"; 1997; Tetrahedron Letters; 38(33); 5869-5872). The Office Action states that the teachings of Watson et al and Clements et al are as outlined above. The Office action further states that Bell et al. teaches that the elected compound (3, 7-diepi-casuarine) is likely to have similar properties to casuarine, since they are diastereomers and, because Watson et al established that casuarine and nectrisine are structurally similar, that one of skill in the art would have expected the elected compound to have immune stimulant properties. Further, the Office Action states that it would have been obvious to one of skill in the art to administer 3, 7-diepi-casuarine along with any of the vaccines taught in Clements et al., giving the method of the instant claims.

As described above, the Watson reference does not establish a structural similarity between casuarine, or the compounds of the present invention, and nectrisine. Further, even if Watson et al. did establish structural similarity, nothing in Watson et al or Clements et al teaches a type-1 specific immune stimulation or the capability to shift an immune response from a type-2 response toward a type-1 response. Nothing in Bell et al. remedies these deficiencies, and thus applicant believes this rejection is inapposite.

The Office Action then states that claims 57-58 are rejected under 35 U.S.C. §103(a) as unpatentable over Watson et al, in view of Clements et al, and in further view of Slovin et al ("Peptide and carbohydrate vaccines in relapsed prostate cancer: immunogenicity of synthetic vaccines in man – clinical trials at Memorial Sloan-Kettering Cancer Center"; 1999; Semin. Oncol. 26(4); 448-454). The Office Action states that the teachings of Watson et al and Clements et al are as outlined above. The Office Action then says that Slovin et al teaches that "men with rising prostate-specific antigen (PSA) levels after primary therapies such as prostatectomy or radiotherapy represent a unique groups for whom no standard treatment option exists; a series of phase I monovalent carbohydrate and glycoprotein-conjugate vaccine trials using the patients' immune system to generate an antitumor response if the focus of the report; these synthetic vaccines are conjugated to keyhole limpet hemocyanin (KLH) and given with the immunologic adjuvant QS21 as five subcutaneous vaccines over 26 weeks; all patients generated specific high-titer immunoglobulin M (IgM) and/or IgG antibodies" (please see Office Action

pages 16-17). Through combining the Watson, Clements and Slovin references, the Office Action states that it would be obvious to one of skill in the art at the time of the present invention to administer swainsonine, nectrisine, or casuarine in place of QS21, via subcutaneous vaccines, giving the method of the instant claims, with the motivation to combine these references being "the expectation of these compounds to provide adjuvant activity in place of QS21 based on the immune stimulatory activity of swainsonine and nectrisine and the structural similarity of casuarine.

As discussed at length above, the structural similarity between the casuarine or other compounds of the present invention is not sufficient to support the assertion that one of skill in the art would understand casuarine to have immune modulatory activity based upon any structural similarity between casuarine and either swainsonine or nectrisine. Also as discussed above, even if the degree of structural similarity were sufficient to support such an assertion, none of the cited references, including Slovin, describe either swainsonine or nectrisine as having the property of stimulating a type-1 immune response or shifting a type-2 immune response toward a type-1 immune response. For these reasons, applicant believes this rejection is inapposite and should be withdrawn.

It is respectfully submitted that the above-identified application is now in a condition for allowance and favorable reconsideration and prompt allowance of these claims are respectfully requested. Should the Examiner believe that anything further is desirable in order to place the application in better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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